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# Total Synthesis of Thromboxane $B_2$ via a Key Bicyclic Enal Intermediate

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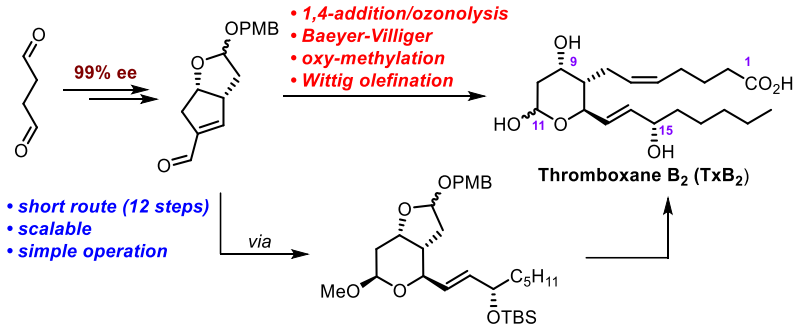
*Supporting Information Placeholder*




**ABSTRACT:** A 12-step asymmetric synthesis of thromboxane $B_2$ ($TxB_2$) from 2,5-dimethoxytetrahydrofuran is described. The synthesis employs our organocatalytic aldol reaction of succinaldehyde to give a key bicyclic enal intermediate. From here, the synthetic strategy involves a conjugate addition of an alkenyl side chain to the bicyclic enal, Baeyer-Villiger oxidation, and a highly *Z*-selective Wittig olefination of hemiacetals. Key to success was selecting the timing of the appropriate oxidation state of the different functional groups.

Thromboxane $B_2$ ($TxB_2$) is a metabolite of thromboxane $A_2$ ($TxA_2$, $t_{1/2}$ (37 °C) = 32 s at pH 7.40), a prostanoid which causes contraction of coronary vessels and platelet aggregation (thrombosis)(Scheme 1).[1] Although $TxB_2$ is generally regarded as biologically inert, there are reports that it inhibits the pulmonary inactivation of $PGE_2$,[2] and that it may play a role in the immune[3] and vascular systems too.[4] It's main use is as a marker for $TxA_2$ and it is recognized as a valuable molecule for the studies of prostanoid-related biochemical processes.[5] For example, Still employed $TxB_2$ as a synthetic precursor to the biologically active $TxA_2$.[5a,6] The interesting molecular architecture of the natural product $TxB_2$ has made it an appealing target for chemists over the years.[7] In this context, several asymmetric syntheses of $TxB_2$ have been reported.[8] However, the previous synthetic strategies are rather lengthy and lack atom economy, costing time and energy, and so improved syntheses are still in demand.

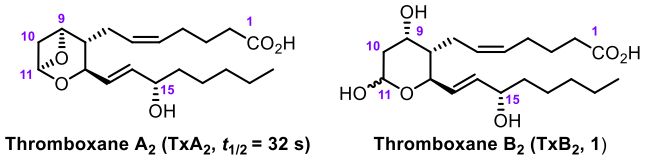
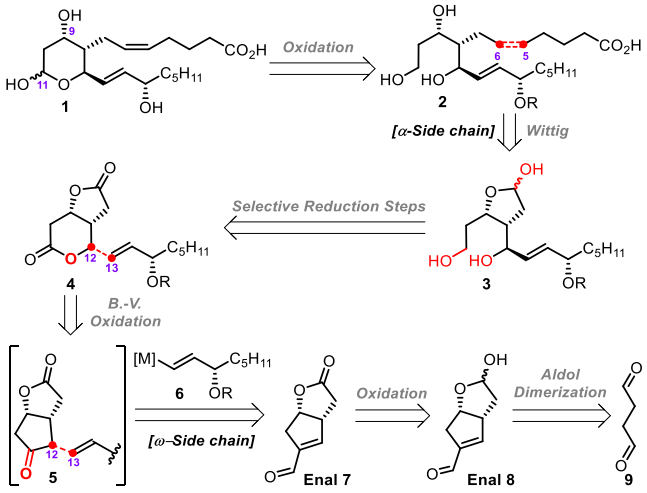



**Figure 1.** Structures of thromboxane $A_2$ and thromboxane $B_2$.

We recently developed a short synthetic strategy to prostaglandins, completing the total synthesis of $PGF_{2\alpha}$ in just 7 steps[9a] and applied this methodology to several prostaglandin-based drugs[9b,9c] and to $\Delta^{12}$-$PGJ_3$.[9d] The key step in the synthesis employed a (*L*)-proline catalysed double aldol dimerization of succinaldehyde to prepare the key bicyclic enal intermediate (**8**).[9a,d] We were keen to broaden the reach of this chemistry and in particular to demonstrate its application to other prostanoids. Just as the Corey lactone[10] has been used for the preparation of a wide range of prostanoids, we see our enal intermediate, **8**, as being perfectly set up for further transformations to access the whole family of prostanoids in an efficient manner. As part of this effort, we now report the application of this strategy to a 12-step synthesis of the natural prostanoid $TxB_2$.[11]

**Scheme 1.** Retrosynthetic analysis of thromboxane $B_2$ from the key bicyclic enal intermediate

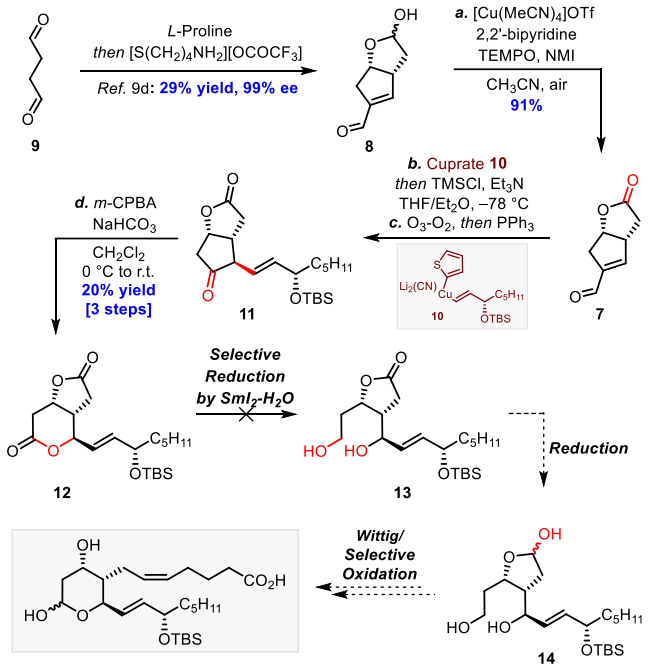



Our retrosynthetic analysis for the stereoselective synthesis of $TxB_2$ is shown in Scheme 1. We envisaged that the α-side chain

could be introduced by a Wittig reaction on the corresponding hemiacetal **3**. This could be obtained by selective reduction of lactone **4**, which itself could be synthesized by Baeyer-Villiger oxidation of ketone **5**. Ketone **5** could be generated from a stereoselective conjugate addition of the chiral ω-side chain **6** to the key enal intermediate **7** followed by ozonolysis. Although selective redox steps are required (**4**→**3**), this analysis was deemed preferable over using the acetal since (i) the lactone is a crystalline compound (ii) it is a single diastereoisomer whereas the acetal is a mixture and (iii) it minimizes the use of protecting groups.

We began our synthesis with the preparation of enal-lactone **7**, available in just 3 steps on multigram scale with high *ee* using our *L*-proline-catalyzed double aldol reaction of succinaldehyde (**9**), generated by hydrolysis of commercially obtainable 2,5-dimethoxytetrahydrofuran (Scheme 2).[9] Subsequent conjugate addition of the mixed vinyl cuprate **10** to **7** followed by trapping with TMSCl and selective ozonolysis[9a,9b] gave ketone **11** which was then converted to the dilactone intermediate **12** *via* Baeyer-Villiger oxidation[12] [20% yield (unoptimized), over 3 steps]. Unfortunately, all attempts to selectively reduce dilactone **12** to the corresponding Wittig reaction precursor **14** *via* the formation of **13** using Proctor's $SmI_2$-$H_2O$ method[13] led to complex reaction mixtures (see SI for detailed information). Although this method had been reported to reduce 6 membered lactones to the diol in the presence of 5 membered ring lactones, we observed the formation of multiple reaction products when applied to dilactone **12**.

**Scheme 2.** Initial attempts to thromboxane $B_2$ *via* the formation of dilactone **12**

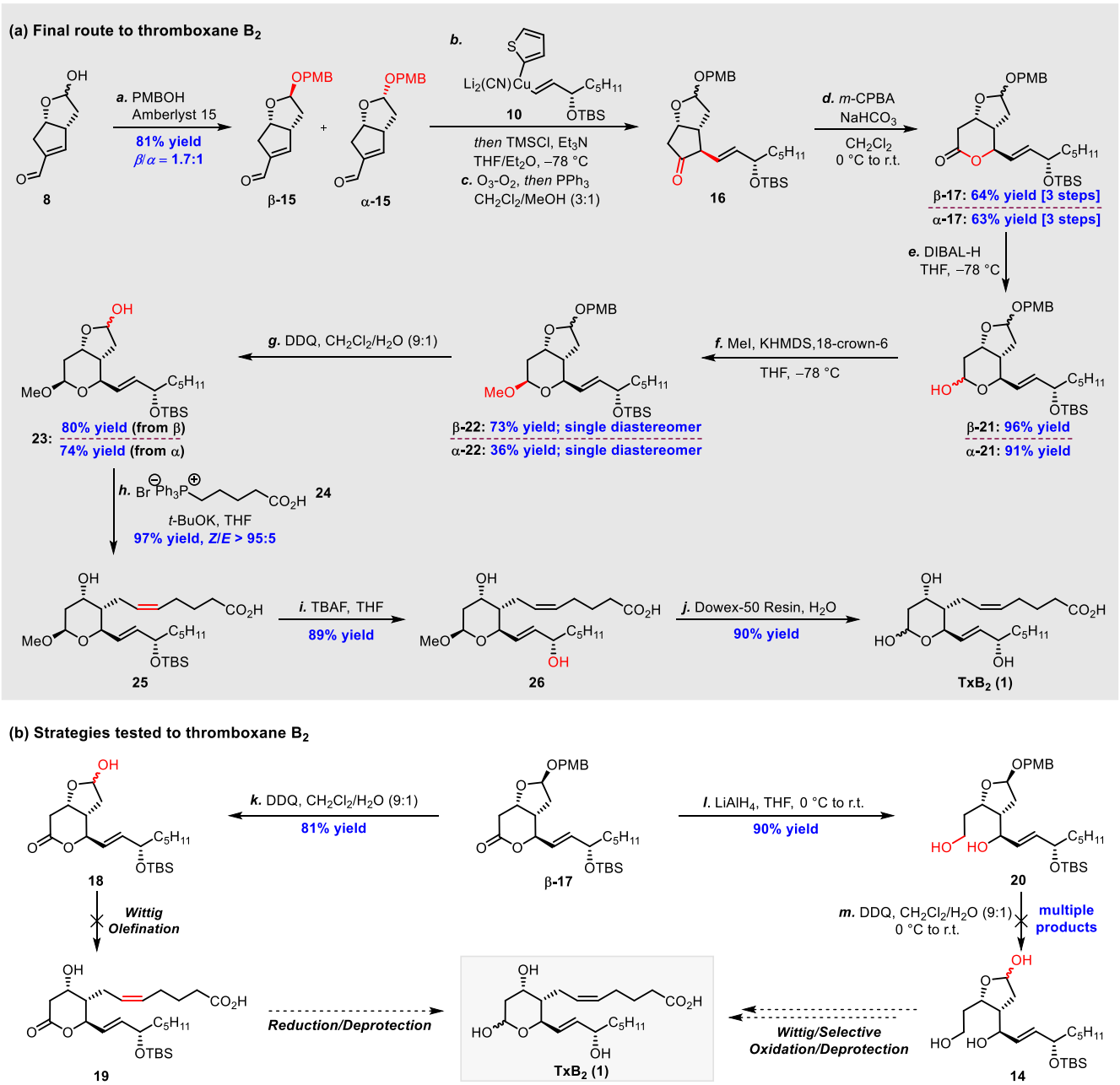



*Reagents and conditions:* (a) $[Cu(MeCN)_4]OTf$ (5 mol %), 2'-Bipyridine (5 mol %), TEMPO (5 mol %), NMI (10 mol %), $CH_3CN$, Air, r.t., overnight, 91% yield. (b) Cuprate **10** (1.2 eq.), THF/$Et_2O$, −78 °C; then TMSCl (5 eq.), $Et_3N$ (6 eq.), −78 °C to −20 °C. (c) $O_3$-$O_2$, $CH_2Cl_2$/MeOH (*v*/*v*, 3:1), −78 °C; then $PPh_3$ (1.5 eq.). (d) *m*-CPBA (2.5 eq.), $NaHCO_3$ (2.7 eq.), $CH_2Cl_2$, 0 °C to r.t., 36 h, 20% yield, 3 steps. TEMPO, 2,2,6,6-tetramethyl-1-piperidinyloxy. NMI, *N*-methylimidazole. TBS, *tert*-butyldimethylsilyl. TMS, trimethylsilyl. *m*-CPBA, *m*-chloroperoxybenzoic acid. DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

Due to the difficulty in selectively reducing one of the two lactones, we decided to begin with the acetal in place, since the hemiacetal is formed directly from the proline catalyzed aldol reaction. Furthermore, this would avoid additional oxidation and reduction steps. We selected the *para*-methoxybenzyl acetal **15** to aid deprotection under neutral conditions (Scheme 3). Although this route has the acetal at the required oxidation state, it is complicated by the having to manipulate and carry through two diastereoisomers. In fact, we found it better to separate the acetal diastereomers and manipulate them separately, as this allowed us to monitor reactions more easily and purify and characterize compounds more fully. Initially, the major β-isomer of the acetals was selected, and we carried through the established 1,4-addition/ozonolysis/Baeyer-Villiger oxidation, delivering the key lactone intermediate β-**17** (64% yield, over 3 steps). Following PMB deprotection with DDQ, we explored the Wittig reaction with (4-carboxybutyl)triphenyl-phosphonium bromide or [4-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)butyl]triphenylphosphonium iodide[14] but these invariably led to intractable mixtures (Scheme 3b). We suspected that under basic conditions, the lactone moiety in intermediate **18** was interfering in this step causing side reactions, and so we decided to remove it. Initially, we considered reduction to the diol since, as shown in Scheme **3b**, this could lead to a short synthesis of $TxB_2$, simply requiring reduction, Wittig reaction, selective oxidation and deprotection. Unfortunately, whilst $LiAlH_4$ reduction to diol **20** was successful we were unable to deprotect the PMB group cleanly.

We therefore considered an alternative strategy in which we conducted a controlled reduction of the lactone to the required oxidation state and employed a protecting group instead, i.e. conversion of lactone β-**17** into the methoxy acetal. Starting with β-**17**, reduction (DIBAL-H, THF, –78 °C) and oxy-methylation of the "naked" anion generated by deprotonation with KHMDS in the presence of 18-crown-6, afforded acetal β-**22** as a single diastereoisomer.[15] The established 1,4-addition/ozonolysis/Baeyer-Villiger oxidation protocol was also applied to the minor α-isomer of PMB-acetals **15**, affording lactone α-**17** in 63% yield over 3 steps. Reduction with DIBAL-H, followed by oxy-methylation again furnished a single diastereomer α-**22**. Interestingly, the α- and β-isomers of hemiacetal **21** showed quite different reactivity: the α-isomer was far more labile under oxy-methylation conditions than the β-isomer giving several un-identified side products (36% yield for α vs. 73% yield for β). Following PMB deprotection of acetals **22** with DDQ, Wittig olefination using phosphonium salt **24** with *t*-BuOK now successfully gave the corresponding alkene **25** in 97% yield with *Z*/*E* > 95:5. Desilylation of the TBS group with TBAF gave the required thromboxane $B_2$ methyl glycoside **26** in 89% yield. Finally, subjecting methyl glycoside **26** to hydrolysis with excess Dowex-50 resin in water, furnished thromboxane $B_2$ ($TxB_2$, **1**) in 90% yield.[16]

**Scheme 3.** Completion of the synthesis of thromboxane $B_2$




*Reagents and conditions:* (a) PMBOH (2 eq.), Amberlyst 15 (cat.), $MgSO_4$ (2.5 eq.), $CH_2Cl_2$, 0 °C to r.t., 24 h; then $MnO_2$ (6 eq.), r.t., 12 h, 81% yield, 1.7:1 β/α. (b) Cuprate **10** (1.2 eq.), THF/$Et_2O$, −78 °C; then TMSCl (5 eq.), $Et_3N$ (6 eq.), −78 °C to −20 °C. (c) $O_3$-$O_2$, $CH_2Cl_2$/MeOH (*v*/*v*, 3:1), −78 °C; then $PPh_3$ (1.5 eq.). (d) *m*-CPBA (2.5 eq.), $NaHCO_3$ (2.7 eq.), $CH_2Cl_2$, 0 °C to r.t., 36 h, 64% yield for β, 63% yield for α, 3 steps. (e) DIBAL-H (3.0 eq.), THF, −78 °C, 3 h, 96% yield for β, 91% yield for α. (f) MeI (3 eq.), KHMDS (1.1 eq.), 18-Crown-6 (1.1 eq.), THF, −78 °C, 18 h, single diastereomer, 73% yield for β, 36% yield for α. (g) DDQ (1.5 eq.), $CH_2Cl_2$/$H_2O$ (*v*/*v*, 9:1), 0 °C to r.t., 6 h, 80% yield for β, 74% yield for α. (h) (4-carboxybutyl)triphenyl-phosphonium bromide (4 eq.), *t*-BuOK (8 eq.), THF, 0 °C to r.t., 2 h, 97% yield with *Z*/*E* > 95:5. (i) TBAF (2 eq.), THF, 0 °C to r.t.,12 h, 89% yield. (j) Dowex-50 Resin, $H_2O$, r.t., 16 h, 90% yield. (k) DDQ (1.5 eq.), $CH_2Cl_2$/$H_2O$ (*v*/*v*, 9:1), 0 °C to r.t., 6 h, 81% yield. (l) $LiAlH_4$ (1.2 eq.), THF, 0 °C to r.t., 6 h, 90% yield. (m) DDQ (1.5 eq.), $CH_2Cl_2$/$H_2O$ (*v*/*v*, 9:1), 0 °C to r.t., 6 h, messy. *p*-methoxybenzyl. TBS, *tert*-butyldimethylsilyl. TMS, trimethylsilyl. *m*-CPBA, *m*-chloroperoxybenzoic acid. DIBAL-H, diisobutylaluminum hydride. HMDS, bis(trimethylsilyl)amide. DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. TBAF, tetrabutylammonium fluoride.

In conclusion, we have developed a highly stereoselective synthesis of thromboxane $B_2$ in 12 steps with an overall yield of 5%, utilizing our key enal intermediate, which is readily available in two steps by a *L*-proline-catalyzed aldol dimerization of succinaldehyde in high ee. The key features include an efficient 1,4-addition/ozonolysis/Baeyer-Villiger oxidation protocol, and a Wittig olefination of hemiacetals with excellent levels of *Z* selectivity. Although carrying through the diastereomeric acetals complicates analysis, it avoids additional redox steps enabling the synthesis to be completed in short order. The synthesis adds to the growing list of

prostanoids that can now be accessed from our key enal intermediate, available on scale in high enantioselectivity in just two steps.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

General procedures, characterization data, and copies of NMR spectra for all novel compounds.

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### Notes

The authors declare no competing financial interests.

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## REFERENCES


(1) (a) Hamberg, M.; Svensson, J.; Samuelsson, B. Thromboxanes: A New Group of Biologically Active Compounds Derived from Prostaglandin Endoperoxides. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72*, 2994-2998. (b) Fried, J.; Zhou, Z.; Chen, C.-K. On the Structure of Thromboxane $A_2$. *Tetrahedron Lett.* **1984**, *25*, 3271–3272.

(2) (a) Boura, A. L. A.; Murphy, R. D. Thromboxane $B_2$ Inhibits Prostaglandin $E_2$ Inactivation by the Rat Isolated Perfused Lung. *Clin. Exp. Pharmacol. Physiol.* **1978**, *5*, 387–392. (b) Fitzpatrick, T. M.; Friedman, L. S.; Kot, P. A.; Ramwell, P. W. Tromboxane $B_2$ Inhibits the Pulmonary Inactivation of Prostaglandin $E_2$ in the Dog. *Br. J. Pharmacol.* **1980**, *70*, 295–299.

(3) Morchón, R.; Carretón, E; García, R.; Zueva, T.; Kartashev, V.; Simón, F. A. Possible Relationship Between Thromboxane $B_2$ and Leukotriene $B_4$ and the Encapsulation of Dirofilaria Repens Worms in Human Subcutaneous Dirofilariasis. *J. Helminthol.* **2019**, *94*, 1–3.

(4) Friedman, L. S.; Fitzpatrick, T. M.; Bloom, M. F.; Ramwell, P. W., Rose, J. C.; Kot, P. A. Cardiovascular and Pulmonary Effects of Thromboxane $B_2$ in the Dog. *Circ Res.* **1979**, *44*, 748–751.

(5) (a) Bhagwat, S. S.; Hamann, P. R.; Still, W. C. Synthesis of Thromboxane $A_2$. *J. Am. Chem. Soc.* **1985**, *107*, 6372–6376. (b) Maddens, B. E.J.; Daminet, S.; Demeyere, K.; Demon, D.; Smets, P.; Meyer, E. Validation of Immunoassays for the Candidate Renal Markers C-Reactive Protein, Immunoglobulin G, Thromboxane $B_2$ and Retinol Binding Protein in Canine Urine. *Vet. Immunol. Immunopathol.* **2010**, *134*, 259–264. (c) Minet, V.; Evrard, J.; Vancraeynest, C.; Dogné, J-M.; Mullier, F.; Pochet, L. Development and Validation of a Liquid Chromatography/Tandem Mass Spectrometry Method for the Simultaneous Quantification of Serotonin and Thromboxane $B_2$ from Activated Platelets. *Int. J. Lab. Hem.* **2018**, *40*, 663–671. (d) Narumiya, S.; Sugimoto, Y.; Ushikubi, F. Prostanoid Receptors: Structures, Properties, and Functions. *Physiol. Rev.* **1999**, *79*, 1193–1226. (e) Breyer, R. M.; Bagdassarian, C. K.; Myers, S. A.; Breyer, M. D. Prostanoid Receptors: Subtypes and Signaling. *Annu. Rev. Pharmacol. Toxicol.* **2001**, *41*, 661–690. (f) Ricciotti, E.; FitzGerald, G. A. Prostaglandins and Inflammation. *Arterioscler. Thromb. Vasc. Biol.* **2011**, *31*, 986–1000.

(6) Bhagwat, S. S.; Hamann, P. R.; Still, W. C.; Bunting, S.; Fitzpatrick, F. A. Synthesis and Structure of the Platelet Aggregation Factor Thromboxane $A_2$. *Nature* **1985**, *315*, 511–513.

(7) Reviews, see: (a) Nicolaou, K. C.; Gasic, G. P.; Barnette, W. E. Synthesis and Biological Properties of Prostaglandin Endoperoxides, Thromboxanes and Prostacyclins. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 293–312. (b) Newton, R. F.; Roberts, S. M. *Synthesis* **1984**, 449–478. (c) Pelyvás, I. F.; Thiem, J.; Tóth, Z. G. Access to Thromboxane Compounds: Syntheses from Carbohydrates, as Natural Chiral Pools. *J. Carbohydr.Chem.* **1998**, *17*, 1–26.

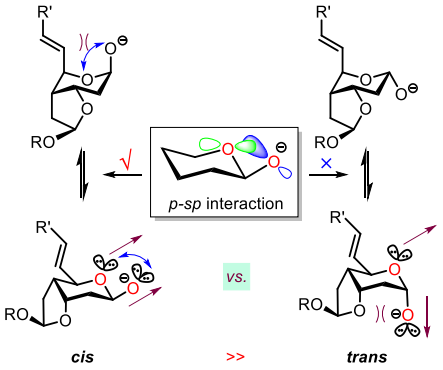
(8) (a) Nelson, N. A.; Jackson, R. W. Total Synthesis of Thromboxane $B_2$. *Tetrahedron Lett.* **1976**, *17*, 3275–3278. (b) Kelly, R. C.; Schletter, I.; Stein, S. J. Synthesis of Thromboxane $B_2$. *Tetrahedron Lett.* **1976**, *17*, 3279–3282. (c) Schneider, W. P.; Morge, R. A. A Synthesis of Crystalline Thrombxane $B_2$ from a Derivative of Prostaglanding $F_{2\alpha}$. *Tetrahedron Lett.* **1976**, *17*, 3283–3286. (d) Corey, E. J.; Shibasaki, M.; Knolle, J.; Sugahara, T. A Direct Total Synthesis of Thromboxane $B_2$ (±). *Tetrahedron Lett.* **1977**, *18*, 785–788. (e) Corey, E. J.; Shibasaki, M.; Knolle, J. Simple, Stereocontrolled Synthesis of Thromboxane $B_2$ from *D*-Glucose. *Tetrahedron Lett.* **1977**, *18*, 1625–1626. (f) Hanessian, S.; Lavallee, P. A Stereospecific, Total Synthesis of Thromboxane $B_2$. *Can. J. Chem.* **1977**, *55*, 562–565. (g) Kelly, A. G.; Roberts, J. S. A Simple, Stereocontrolled Synthesis of a Thromboxane $B_2$ Synthon. *J. Chem. Soc., Chem. Commun.* **1980**, 228–229. (h) Hanessian, S.; Lavallee, P. Total Synthesis of (+)-Thromboxane $B_2$ from *D*-Glucose. A Detailed Account. *Can. J. Chem.* **1981**, *59*, 870–877. (i) Basson, M. M.; Holzapfel, C. W.; Verdoorn, G. H. Palladium Assisted Synthesis of a Thromboxane $B_2$ Precursor. *Heterocycles* **1989**, *29*, 2261–2265. (j) Masaki, Y.; Yoshizawa, K.; Itoh, A. Total Synthesis of Thromboxane $B_2$ Starting from (*R,R*)-Tartaric Acid as a Chiral Pool. *Tetrahedron Lett.* **1996**, *37*, 9321–9324. (k) Marvin, C. C.; Clemens, A. J. L.; Burke, S. D. Synthesis of Thromboxane $B_2$ via Ketalization/Ring-Closing Metathesis. *Org. Lett.* **2007**, *9*, 5353–5356.

(9) (a) Coulthard, G.; Erb, W.; Aggarwal, V. K. Stereocontrolled Organocatalytic Synthesis of Prostaglandin $PGF_{2\alpha}$ in Seven Steps. *Nature* **2012**, *489*, 278–281. (b) Prévost, S.; Thai, K.; Schützenmeister, N.; Coulthard, G.; Erb, W.; Aggarwal, V. K. Synthesis of Prostaglandin Analogues, Latanoprost and Bimatoprost, Using Organocatalysis via a Key Bicyclic Enal Intermediate. *Org. Lett.* **2015**, *17*, 504–507. (c) Baars, H.; Classen, M. J.; Aggarwal, V. K. Synthesis of Alfaprostol and $PGF_{2\alpha}$ through 1,4-Addition of an Alkyne to an Enal Intermediate as the Key Step. *Org. Lett.* **2017**, *19*, 6008–6011. (d) Pelšs, A.; Gandhamsetty, N.; Smith, J. R.; Mailhol, D.; Silvi, M.; Watson, A. J. A.; Perez-Powell, I.; Prévost, S.; Schützenmeister, N.; Moore, P. R.; Aggarwal, V. K. Re-optimization of the Organocatalyzed Double Aldol Domino Process to a Key Enal Intermediate and Its Application to the Total Synthesis of $\Delta^{12}$-Prostaglandin $J_3$. *Chem. Eur. J.* **2018**, *24*, 9542–9545. (e) Bennett, S. H.; Coulthard,G.; Aggarwal, V. K. Prostaglandin Total Synthesis Enabled by the Organocatalytic Dimerization of Succinaldehyde, *Chem. Rec.* **2020**, DOI: 10.1002/tcr.202000054

(10) Reviews, see: (a) Das, S.; Chandrasekhar, S.; Yadav, J. S.; Grée, R. Recent Developments in the Synthesis of Prostaglandins and Analogues. *Chem. Rev.* **2007**, *107*, 3286–3337. (b) Simeonov, S. P.; Nunes, J. P. M.; Guerra, K.; Kurteva, V. B.; Afonso, C. A. M. Synthesis of Chiral Cyclopentenones. *Chem. Rev.* **2016**, *116*, 5744–5893. (c) Peng, H.; Chen, F.-E. Recent Advances in Asymmetric Total Synthesis of Prostaglandins. *Org. Biomol. Chem.* **2017**, *15*, 6281–6301. For selected pioneering articles see: (d) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. Stereo-controlled Synthesis of Prostaglandins $F_{2\alpha}$ and $E_2$. *J. Am. Chem. Soc.* **1969**, *91*, 5675–5677. (e) Corey, E. J.; Schaaf, T. K.; Huber, W.; Koelliker, U.; Weinshenker, N. M. Total Synthesis of Prostaglandins $F_{2\alpha}$ and $E_2$ as the Naturally Occuring Forms. *J. Am. Chem. Soc.* **1970**, *92*, 397–398. (f) Corey, E. J.; Noyori, R.; Schaaf, T. K. Total Synthesis of Prostaglandins $F_{1\alpha}$, $E_1$, $F_{2\alpha}$, and $E_2$ (Natural Forms) from a Common Synthetic Intermediate. *J. Am. Chem. Soc.* **1970**, *92*, 2586–2587. (g) Corey, E. J. Studies on the Total Synthesis of Prostaglandins. *Ann. N. Y. Acad. Sci. 1971*, 180, 24–37.

(11) We have recently completed the synthesis of the non-natural fluorinated analogues of Thromboxane $A_2$; see: Jing, C.; Mallah, S.;

Kriemen, E.; Bennett, S. H.; Fasano, V.; Lennox, A. J. J.; Hers, I.; Aggarwal, V. K. Synthesis, Stability, and Biological Studies of Fluorinated Analogues of Thromboxane $A_2$. *ACS Cent. Sci.* **2020**, *6*, 995–1000.
(12) (a) Forster, A.; Fitremann, J.; Renaud, P. Preparation of An Advanced Intermediate for the Synthesis of *epi*-Thromboxanes. *Tetrahedron Lett.* **1998**, *39*, 3485–3488. (b) Leonard, J.; Ouali, D.; Rahman, S. K. A Short Enantioselective Route to Corynanthe Alkaloid Precursors. *Tetrahedron Lett.* **1990**, *31*, 739–742.
(13) Duffy, L. A.; Matsubara, H.; Procter, D. J. A Ring Size-Selective Reduction of Lactones Using $SmI_2$ and $H_2O$. *J. Am. Chem. Soc.* **2008**, *130*, 1136–1137.
(14) Martynow, J. G.; Jóźwik, J.; Szelejewski, W.; Achmatowicz, O.; Kutner, A.; Wiśniewski, K.; Winiarski, J.; Zegrocka-Stendel, O.; Gołębiewski, P. A New Synthetic Approach to High-Purity (15*R*)-Latanoprost. *Eur. J. Org. Chem.* **2007**, 689–703.
(15) Although the diastereoselectivity of the alkylation is inconsequential, it is noteworthy nonetheless and can be accounted for as follows. The repulsion between the oxygen lone pairs as well as overlapping of a *p*-type orbital of the ring oxygen and s*p*-type orbital of the exocyclic oxygen, increases the nucleophilicity of the *cis*-O-"naked" anion generated from alkoxide *β*-**21** upon deprotonation. However, a similar enhancement in reactivity is not expected for *trans*-O-"naked" anion (See Figure below).




For selected articles, see (a) Adderley, N. J.; Buchanan, D. J.; Dixon, D. J.; Lainé, D. I. Highly Diastereoselective Oxy-Michael Additions of Enantiopure *δ*-Lactol Anions to Nitroalkenes: Asymmetric Synthesis of 1,2-Amino Alcohols. *Angew. Chem. Int. Ed.* **2003**, *42*, 4241–4244. (b) Buchanan, D. J.; Dixon, D. J.; Hernandez-Juan, F. A. Highly Stereoselective Intermolecular Oxy-Michael Addition Reaction to *α,β*-Unsaturated Malonate Esters. *Org. Lett.* **2004**, *6*, 1357–1360. (c) Webb, D.; van den Heuvel, A.; Kögl, M.; Ley, S. V. Enantioselective Synthesis of the Lyngbouilloside Macrolactone Core. *Synlett* **2009**, 2320–2324. For further evidence of the mechanism, see (d) Schmidt, R. R.; Michel, J. Direct *O*-Glycosyl Trichloroacetimidate Formation, Nucleophilicity of the Anomeric Oxygen Atom. *Tetrahedron Lett.* **1984**, *25*, 821–824. (e) Fraser-Reid, B.; Mootoo, D. R.; Konradsson, P.; Udodong, U. E.; Andrews, C. W.; Ratcliffe, A. J.; Wu, Z.; Yu, K. L. Novel Carbohydrate Transformations Discovered En Route to Natural Products. *Pure Appl. Chem.* **1989**, *61*, 1243–1256. (f) Dixon, D. J.; Ley, S. V.; Tate, E. W. Diastereoselective Oxygen to Carbon Rearrangements of Anomerically Linked Enol Ethers and the Total Synthesis of (+)-(*S*,*S*)-(*cis*-6-Methyltetrahydropyran-2-yl)acetic Acid, A Component of Civet. *J. Chem. Soc. Perkin Trans. 1*, **2000**, 2385–2394.
(16) We obtained full spectroscopic data ($^1$H NMR, $^{13}$C NMR, HRMS, and $[\alpha]_D^{24}$) of the methyl glycoside, but obtaining high quality data for $TxB_2$ itself was more challenging. We were able to obtain HRMS (see SI), mp. 91-94 °C, and $[\alpha]_D^{24}$ = +57.10 (*c* 1.0, EtOH) which matched the literature [lit.[8b] mp. 92.0-92.5 °C, $[\alpha]_D$ = +56.50 (*c* 1.0, EtOH)]. However, $^1$H NMR spectrum of our sample was somewhat broad with multiple peaks, reflecting perhaps different aggregation states of the molecule in $CDCl_3$. This has been documented in previous syntheses of $TxB_2$.[8k] For comparison, we have included the $^1$H NMR of our sample with that of a commercial sample from Cayman in the SI.